UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte PETER M. GLAZER

Appeal No. 2006-2149
Application No. 09/978,333

HEARD: August 8, 2006

Before SCHEINER, ADAMS and MILLS, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to triplex-forming oligonucleotide-mediated recombination between target and donor nucleic acid molecules. Claims 7-12 and 15-25, all the claims remaining in the application, stand rejected as nonenabled. In addition, claims 7-12 and 25 stand rejected as anticipated.[1] We have jurisdiction under 35 U.S.C. § 134. We will reverse the enablement rejection, but affirm the anticipation rejection.

[1] The examiner withdrew several rejections in the Examiner's Answer: the rejection of claims 15-24 under 35 U.S.C. § 112, second paragraph; the rejection of claims 15-21, 23 and 24 under 35 U.S.C. § 102(b); and the rejection of claim 22 under 35 U.S.C. § 103.

Background

"[O]ligonucleotides can bind as third strands of DNA in a sequence specific manner in the major groove in polypurine/polypyrimidine stretches in duplex DNA" (Specification, page 1), "forming a triplex region" (id., page 5). "The binding of the oligonucleotide to [a] target region stimulates mutations within or adjacent to the target region using cellular DNA synthesis, recombination, and repair mechanisms. The mutation generated activates, inactivates, or alters the activity and function of the target gene." Id.

High affinity, triplex-forming oligonucleotides (TFOs) "can further be used to stimulate homologous recombination of a separate DNA fragment into the target region. The [TFO] activates cellular DNA synthesis, recombination, and repair mechanisms through triple helix formation. The activated cellular mechanisms can be directed to recombine a second DNA fragment into the target region. The second DNA fragment may be tethered to the oligonucleotide or physically separate." Id., page 7.

According to appellant, Example 1 of the specification demonstrates targeted triplex-induced recombination in a cell-free extract of monkey COS cells using a donor oligonucleotide fragment tethered to a TFO, while Example 2 demonstrates targeted triplex-induced recombination in HeLa cell-free extracts. Finally, according to appellant, Example 6 demonstrates mutagenesis "at specific genomic sites in somatic cells of adult mice . . . treated with a [targeted] TFO" (Specifiation, page 31) and Example 7 demonstrates heritable changes in mice as a result of triplex-induced site specific mutagenesis (id., pages 15-17, 27, 28, and 31-34).

Discussion

The Claims

Claims 7-12 and 15-25 are pending. Claims 7, 9, 15 and 21 are representative and read as follows:

7. A method for targeted recombination of a nucleic acid molecule comprising the steps of:
a) providing a single-stranded oligonucleotide having a sequence that forms a triple-stranded nucleic acid molecule by hybridizing with a target sequence in a double-stranded nucleic acid molecule with a Kd of less than or equal to 2×10^{-7}; and
b) providing a donor nucleic acid such that recombination of the donor nucleic acid into the target sequence is induced by triple helix formation between the single-stranded oligonucleotide and the double-stranded nucleic acid molecule.

9. The method of claim 7, wherein the single-stranded oligonucleotide is tethered to the donor nucleic acid.

15. The method of claim 7 to produce changes in the genome of an intact human or animal wherein
the single-stranded oligonucleotide is administered into an intact human or animal having a sequence that forms a triple-stranded nucleic acid molecule with the target sequence located in the genome of an intact human or animal, wherein the oligonucleotide binds to the target sequence with a Kd of less than or equal to 2×10^{-7}, and mutates the target sequence.

21. The method of claim 15 wherein the target sequence is selected from the group consisting of a gene, an oncogene, a defective gene, a viral genome, and a portion of a viral genome.

We note that claim 7 encompasses both in vitro and in vivo methods of TFO-targeted recombination, while claim 15 is limited to an in vivo method. Claim 7 also encompasses methods wherein the TFO and donor nucleic acid molecules are tethered or untethered, while claim 9 specifies that they are tethered.

Enablement

The examiner rejected claims 7-12 and 15-25, all of the claims pending, under 35 U.S.C. § 112, first paragraph, for lack of enablement. The examiner argues that the

specification is "enabling for . . . targeted recombination of a target nucleic acid molecule in vitro or ex vivo" (Examiner's Answer, page 4), but "does not reasonably provide enablement for methods of in vivo targeted recombination using a donor nucleic acid and a TFO" (id.), largely because "there is insufficient guidance [ ] in the specification as to how to use . . . [TFOs and donor] oligonucleotides for therapeutic purposes in vivo" (id., page 7).

The examiner acknowledges that targeted recombination was observed in HeLa cell extracts treated with a TFO and a donor fragment. Examiner's Answer, paragraph bridging pages 5-6. The examiner also acknowledges that "mutagenesis was observed in liver, skin, kidney, colon, small intestine and lung cells [of mice treated with a TFO] at a frequency five fold that of background" (id., page 6).

Nevertheless, the examiner argues that the in vitro examples presented in the specification are not predictive of activity in vivo because

> (i) The triple-helix forming oligonucleotides and donor nucleic acids may be degraded in blood and tissues under physiological conditions and [ ] may not reach the target site in sufficient quantities to induce recombination; (ii) The ability of the oligonucleotide to be taken up by the cell is expected to be different under physiological conditions as versus tissue culture . . . (iii) It is not clear what would be the optimum concentration of the oligonucleotide required for effective treatment, the mode of administration and the pharmacokinetics of therapy . . . [(iv) The ability of the oligonucleotide to form a triple helix under physiological conditions . . . varies significantly with oligonucleotide length, and chemical composition and is highly affected by the presence of secondary and tertiary nucleic acid structures; and [(v)] the ability of the donor oligonucleotide to bind to and recombine with the target nucleic acid varies significantly with the length an chemical composition of the donor oligonucleotide and . . . is also affected by secondary and tertiary nucleic acid structures."

Id., pages 6-7.

Moreover, the examiner accords the in vivo examples (Examples 6 and 7) little or no weight because none of them uses "a TFO and donor nucleic acid . . . in combination to induce targeted recombination in an intact human or animal" (id., page 6).

Finally, the examiner cites several references as evidence that TFOs "induce a scattered spectrum of mutations, rather than specific mutations" (id., page 8), which "would not provide an art recognized acceptable means for the treatment of a disease" (id., pages 8-9). Similarly, the examiner cited a number of references as evidence that "it is also highly unpredictable as to whether the TFO/donor oligonucleotide would be capable of inducing a sufficient amount of recombination and mutations in a sufficient quantity of cells to impart a therapeutic effect" (id., page 9).

The examiner concludes that "it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed" (id., page 12), "in view of the breadth of the claims, the recognized unpredictability in the art of targeted recombination and mutagenesis and . . . of the in vivo administration of TFO/donor oligonucleotides, and in view of the lack of working examples in the specification" (id.).

Appellant argues essentially that "the claims do not require therapeutic efficacy" (Reply Brief, page 2), and at most specify "that the method . . . is carried out to produce changes in the genome of an intact human or animal" (id., page 6). Moreover, appellant argues that Examples 6 and 7 of the specification demonstrate that "injection of [a] TFO [into a mouse] resulted in site-directed mutagenesis in vivo as predicted from the in vitro data" and "[t]here has been no evidence provided by the examiner that the evidence in the specification would not be predictive of an oligonucleotide which further included a donor nucleic acid" (id., page 5).

The examiner bears the initial burden of showing that a claimed invention is nonenabled. "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). "When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application." In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

In this case, the examiner has done a thorough and commendable job of explaining her reasons for believing that practicing the claimed method would have required undue experimentation. The examiner has also provided evidence to support her position and clearly explained the relevance of the evidence to the claimed method. Notwithstanding the examiner's diligence, however, we conclude that the rejection is based on an improperly stringent legal standard and must be reversed.

"[E]nablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.' . . . That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991).

"Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field become useful is well before it is ready to be administered to humans." In re Brana, 51 F.3d 1560, 1568, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995). (While the Brana court referred to "usefulness", the rejection on appeal was for nonenablement. See id. at 1564, 34 USPQ2d at 1439.)

The invention that must be enabled to satisfy § 112 is the invention defined by the claims. See CFMT, Inc. v. Yieldup Int'l Corp., 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003) ("Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect."). Thus, when the claims are not limited to a method that achieves therapeutic or clinical efficacy, such efficacy is not required for the claims to be enabled.

Here, the claims are directed to a "method for targeted recombination of a nucleic acid molecule" (claim 7), and a method "to produce changes in the genome of an intact animal" (claim 15). Thus, while it is fair to say that the claims encompass a method that achieves a clinically effective therapeutic response, they do not require it. Cf. In re Cortright, 165 F.3d 1353, 49 USPQ2d 1464 (Fed. Cir. 1999) (claims to a method of "treating scalp baldness" could be enabled even if the method did not produce a full head of hair).

Finally, in our opinion, the examiner has not adequately explained why in vivo Examples 6 and 7 are not relevant to the examiner's concerns regarding the shortcomings of the in vitro examples. That is, the in vivo examples, even though they

do not include a donor nucleic acid, would seem to complement the in vitro examples with respect to the ability of oligonucleotides (TFO or donor) to "reach the target site" under physiological conditions, "the ability . . . to be taken up by [a] cell" under physiological conditions, and "the ability . . . to form a triple helix under physiological conditions[,]" etc. (Examiner's Answer, page 7).

We conclude that the potential problems identified by the examiner may indeed complicate treatment of a patient with TFOs and donor nucleic acids, but such problems need not be overcome in order to "produce changes in the genome of an intact human or animal" - all that is required by the claims. Thus, the examiner has not adequately explained why practicing the claimed method would have required undue experimentation. The rejection under 35 U.S.C. § 112, first paragraph, is reversed.

Anticipation

Claims 7-12 and 25 stand rejected under 35 U.S.C. § 102(b) as anticipated by Chan.[2] Appellant does not dispute that Chan describes the subject matter of these claims, but argues that "Chan is not prior art as the present application is entitled to a priority date of 1995" based on the filing dates of parent applications 09/411,291 and 08/476,712, now U.S. Patents 6,303,376 (the '376 patent) and 5,692,426 (the '426 patent), respectively (Brief, page 15).[3]

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[2] Chan et al., "Targeted Correction of an Episomal Gene in Mammalian Cells by a Short DNA Fragment Tethered to a Triplex-forming Oligonucleotide," The Journal of Biological Chemistry, Vol. 274, No. 17, pp. 11541-11548 (April 23, 1999).

[3] According to appellant, "[t]he present application is a continuation-in-part of U.S.S.N. 09/411,291 filed on October 4, 1999[, now U.S. Patent No. 6,303,376], which is a divisional of U.S.S.N. 08/476,712 filed on June 7, 1995[, now U.S. Patent No. 5,962,426]." Brief, page 15.

In order for a claim in a pending patent application to be entitled to benefit of the earlier filing date of an application under 35 U.S.C. § 120, the earlier application must describe the invention now claimed in the manner provided by the first paragraph of 35 U.S.C. § 112, that is, appellant must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession [of] . . . whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1564, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An issue arising under the written description requirement of 35 U.S.C. § 112, first paragraph, is a question of fact. Id. at 1563, 19 USPQ2d at 1116.

"As to given claimed subject matter, only one effective date is applicable." In re Van Langenhoven, 458 F.2d 132, 136, 172 USPQ 426, 429 (CCPA 1972). The court also observed in Van Langenhoven:

> To be entitled to the filing date of a previously filed application, appellant's application on appeal would have to satisfy the requirements of 35 U.S.C. 120, among which is the requirement that the subject matter now claimed be disclosed in the manner prescribed by the first paragraph of section 112 in the prior application. Since, to conform to section 112, claimed subject matter must be described in the specification relied upon, subject matter which is first disclosed in a continuation-in-part application is not entitled to the filing date of the parent application. Martin v. Johnson, . . . 454 F.2d 746, 172 USPQ 391 ([CCPA] 1972); In re Lukach, 58 CCPA 1233, 442 F.2d 967, 169 USPQ 795 (1971).

According to the examiner, the rejected claims "are [only] entitled to the filing date of [ ] the present application[,] October 15, 2001" (Examiner's Answer, page 20), because "the '376 and '426 patents do not provide support for the concept of a TFO tethered to a donor nucleic acid" (id., page 21). As discussed above, each of the rejected claims either encompasses or requires the use of a tethered donor nucleic acid.

Appellant argues that "[t]he '376 patent discloses at least at column 3, lines 49-56, that TFOs can be used to stimulate recombination of a DNA fragment into a target region, but does not distinguish between whether the DNA fragment is linked or unlinked" and "at least at the paragraph spanning column 1 to column 2, the '376 patent discloses that TFOs are useful alone or linked to reactive moieties" (Brief, page 18).

Nevertheless, we agree with the examiner that the '376 and '426 patents do not provide support for the concept of a TFO tethered to a donor nucleic acid. The paragraph spanning columns 1 and 2 of the '376 patent merely teaches that TFOs may be used "in conjunction with DNA modifying enzymes" or may be linked to "reactive moieties such as EDTA-Fe(II)" or "intercalating agents such as acridine, or to cross-linking agents, such as p-azidophenylacyl and psoralen . . . to enhance the stability of triplex binding." None of these "reactive moieties" have anything in common with the donor fragment. In any case, the '376 patent states quite plainly that TFOs can "be used to stimulate homologous recombination of a separate heterologous DNA fragment into the target region" ('326 patent, column 3, lines 49-52, emphasis ours), while the present application, for the first time, teaches that the donor "DNA fragment may be tethered to the [TFO] or physically separate" (Specification, page 7).

Moreover, even if we were to accept appellant's assertion that "the concept of using TFOs tethered or untethered to a donor nucleic acid would be obvious to one of skill in the art based on the level of knowledge in the art and the disclosure provided in the '376 and '426 patents" (Reply Brief, page 1), obviousness is not sufficient to establish possession of the invention. See Lockwood v. American Airlines Inc., 107 F.3d 1565, 1571-1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) (citations omitted):

> It is the disclosures of the applications that count. Entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed . . . Although the exact terms need not be used in haec verba, . . . the specification must contain an equivalent description of the claimed subject matter.
> . . .
> It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure . . . would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose. Each application in the chain must describe the claimed features.

The examiner further finds that the '376 and '426 patents do not provide written descriptive support for "[a] donor nucleic acid [ ] at least 30 nucleotides in length or [ ] between 10 to 40 nucleotides" (Examiner's Answer, page 23). Inasmuch as the parent patents say nothing at all about the length of a donor nucleic acid fragment, we agree with the examiner.

In addition, the examiner finds that the '376 and '426 patents do not provide written descriptive support for "a TFO having a Kd of less than or equal to 2×10^{-7}" (Examiner's Answer, page 21). Appellant points out that "[the] results in Table 1 demonstrate that TFOs with Kd's of 3×10^{-7} or less result in mutagenesis induced by triple helix formation" (Reply Brief, page 8), and argues that "2×10^{-7} is obviously less than 3×10^{-7}, [thus] dissociation constants of less than or equal to 2×10^{-7} are supported by the '376 patent" (id.). Again, we agree with the examiner. Obviousness is not sufficient to establish possession of the specific dissociation constant recited in the present claims.

Having carefully considered the disclosures of the '376 and '426 patents, we find that they fail to convey with reasonable clarity to those skilled in the art that appellant

was in possession of the present invention at the time the application was filed. We are in agreement with the examiner that claims 7-12 and 25 do not enjoy written descriptive support in the parent applications, and, therefore, are not entitled to the 1995 filing date of the '426 patent under 35 U.S.C. § 120.

Having found that Chan constitutes legally available prior art, we find no error in the examiner's determination that claims 7-12 and 25 are anticipated by Chan. The rejection under 35 U.S.C. § 102(b) is affirmed.

SUMMARY

The rejection of claims 7-12 and 15-25 as non-enabled is reversed, while the rejection of claims 7-12 and 25 as anticipated is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART

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